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Moderate alcohol consumption is associated with lower risk for incident diabetes and mortality: the Hoorn Study

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Abstract

In the present study we examined the association between baseline alcohol consumption and 10-year mortality in subjects with normal and abnormal glucose levels (diabetes, impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)). Furthermore, we assessed the 6-year cumulative incidence of diabetes in categories of alcohol consumption. In the Hoorn Study, which started in 1989, alcohol intake was assessed by questionnaire in 2393 subjects who were subsequently categorised into four groups of alcohol consumption (non-drinkers, up to 10 g per day, 10–30 and ≥ 30 g per day). Glucose tolerance status by oral glucose tolerance test was classified according to the WHO-1999 diagnostic criteria. Subjects who drank up to 10 g per day of alcohol had the lowest mortality risk. The age- and sex-adjusted mortality risks for non-drinkers were 1.55 (1.04–2.32) for subjects with normal glucose levels and 1.72 (1.05–2.82) for subjects with abnormal glucose levels. The risk of diabetes was also lowest for subjects who consumed up to 10 g per day: 8.0 versus 12.9% for non-drinkers ($P < 0.05$). Higher alcohol intakes were associated with increasing risks for mortality and diabetes. Adjustment for classical cardiovascular risk factors and other lifestyle variables did not materially affect the estimates. In conclusion, moderate alcohol consumption was associated with a lower risk for mortality and diabetes.

Keywords: Alcohol; Mortality; Cumulative incidence; Glucose; Diabetes

1. Introduction

Numerous studies have demonstrated a J-shaped relationship between alcohol consumption and mortality in the general population, with the lowest risks for mortality observed with light to moderate alcohol consumption [1–4]. Possible mechanisms for this protective effect of moderate alcohol consumption include beneficial effects on high-density lipoprotein, platelet aggregation and fibrinolytic activity [5–7].

Subjects with diabetes or elevated fasting or postload glucose have an increased risk for all-cause mortality compared with subjects with nor-

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mal glucose levels [8,9]. As in the Nurses' Health Study the beneficial effect of moderate alcohol consumption was highest in those with an increased risk of cardiovascular disease [10], it might be expected that diabetic subjects profit more from moderate alcohol consumption than the general population. As far as we know, only three prospective cohort studies have been performed among diabetic subjects until now [11–13]. These studies showed an inverse association between alcohol consumption and coronary heart disease (CHD) mortality, but did not report on the risks associated with higher alcohol consumption.

As moderate alcohol consumption also beneficially affects insulin sensitivity and glucose metabolism [14,15], several studies have been performed to study the effect of alcohol consumption on the incidence of diabetes. In some of these studies the association was J-shaped, with the lowest incidence of diabetes in subjects with moderate alcohol consumption [16,17], while others observed an overall positive [18] or an inverse association [19,20]. However, because of differences in the diagnosis of diabetes and the range of alcohol intake, it is difficult to compare these studies directly.

In the present study, we investigated the association between alcohol consumption and all-cause mortality in subjects with normal and abnormal glucose levels at baseline. Furthermore, in the same population we assessed the risk of diabetes associated with alcohol consumption.

2. Materials and methods

2.1. Study population; baseline and follow-up measurements

The Hoorn Study is a population-based cohort study on glucose intolerance in a general Dutch elderly population [21]. In 1989, a random sample of all inhabitants of Hoorn aged 50–75 were invited to participate in the study. Of the eligible subjects, 71.5% agreed to participate, resulting in the Hoorn Study cohort of 2484 participants. In the present study, analyses concerning mortality have been performed in 2393 subjects, because of missing values for glucose levels or alcohol consumption. The population register of the city of Hoorn provided information on vital status.

Between January 1996 and December 1998, the majority ($n = 2086$) of the initial cohort was invited to participate in follow-up measurements. Of the original cohort, 108 subjects had moved out of Hoorn, 150 subjects had died before 1996 and 140 subjects were not invited for logistic reasons. A total of 1513 subjects (72.5%) participated. In the present study the analyses concerning the cumulative incidence of diabetes have been done in 1322 participants of the follow-up measurements who did not have diabetes or missing information on alcohol intake at baseline.

The Ethics Committee of the Vrije Universiteit Medical Centre Amsterdam approved the Hoorn Study and written informed consent was obtained from all participants.

2.2. Glucose measurements

Both at baseline and at follow-up fasting glucose and glucose 2 h after a 75 g oral glucose load were determined by a glucose dehydrogenase method (Merck, Darmstad, Germany). Subjects were classified according to the criteria of the WHO Consultation of 1999 [22]. Diabetes was diagnosed if fasting plasma glucose was ≥ 7.0 mmol/l or postload glucose ≥ 11.1 mmol/l. Subjects already treated for diabetes by a general practitioner or clinician (either glucose lowering medication or a diet) were also categorised as diabetic subjects. A fasting plasma glucose between 6.1 and 7.0 mmol/l is defined as impaired fasting glucose (IFG), while a postload glucose level between 7.8 and 11.1 mmol/l is defined as impaired glucose tolerance (IGT) [22]. Abnormal glucose levels were defined as either diabetes, IFG or IGT.

2.3. Alcohol consumption

Information about nutritional habits was obtained by a validated semi-quantitative food frequency questionnaire, including questions about alcohol consumption [23]. Subjects were asked

whether they drank alcohol and if so, how many glasses of various types of alcoholic beverages they consumed a week. This information was converted using a computerised version of the Dutch Food Composition Table [24]. Subjects were categorised in four groups of alcohol consumption: non-drinkers, up to 10 g per day, 10–30 g per day and more than 30 g per day. In the analyses concerning the cumulative incidence of diabetes, the two highest categories of alcohol consumption were taken as one category (≥ 10 g per day), because of small numbers.

2.4. Other measurements

Sitting blood pressure was measured twice on the right arm with a random-zero sphygmomanometer (Hawksley–Gelman, Lancing, UK). The average was used for analyses. Subjects were considered hypertensive if systolic blood pressure was ≥ 160 mmHg, diastolic blood pressure ≥ 95 mmHg, or when using anti-hypertensive medication [25]. Weight and height were measured with subjects wearing light clothes only, and the body mass index (BMI) was calculated as weight/height squared (kg/m^2). Waist and hip circumferences were measured according to a standardised procedure [26], and the waist-to-hip ratio (WH-ratio) was defined as waist circumference divided by hip circumference. Fasting specific insulin level was quantified with an insulin-specific double-antibody radio-immunoassay (antibody SP21; Linco, St. Louis, MO). Triglycerides, total cholesterol and high-density lipoprotein cholesterol (HDL-C) were determined from fasting blood samples by enzymatic techniques (Boehringer Mannheim, Mannheim, Germany). Information on smoking habits and physical activity was obtained by questionnaire. Information on prevalent cardiovascular diseases was obtained using a translated version of the Rose questionnaire from the London School of Hygiene [27].

2.5. Statistical analyses

Differences in baseline characteristics in categories of alcohol consumption were tested by analysis of covariance in case the variables were continuous and normally distributed (adjusted for age and sex). Differences in proportions were tested with logistic regression. Fasting specific insulin and triglycerides were log-transformed before testing, because of the skewed distribution of these variables.

Mortality was expressed as the number of subjects who died per 1000 person years of follow-up. Age- and sex-adjusted relative risks (RRs) (hazard ratios) and 95%-confidence intervals (CI) were estimated using Cox' proportional hazards model. In a second model we adjusted additionally for confounding factors: cigarette smoking (yes or no), participation in sport activities, prevalent cardiovascular disease and hypertension. Subsequently, we also included HDL-C, insulin, triglycerides and WH-ratio as possible intermediate variables in the causal chain linking alcohol to mortality. The reference category was the category of moderate drinkers (up to 10 g per day). All regression models were stratified for normal and abnormal glucose levels.

The cumulative incidence of diabetes was calculated as the proportion of subjects who had developed diabetes at the follow-up measurements. Logistic regression was used to calculate odds ratios (OR). The same possible confounding and intermediate variables in the models for mortality were used. All P values were based on two-sided tests, and the cut-off for statistical significance was 0.05.

3. Results

A total of 1637 subjects (68.4%) reported regular alcohol consumption, varying from 0.7 up to 98.0 g per day (mean 13.0 g per day). For men the mean alcohol consumption was 15.6 g per day, for women 9.7 g per day.

The category of 756 subjects who did not drink alcohol mainly consisted of women (75%). Compared with the subjects who reported moderate alcohol consumption (< 10 g per day), these subjects were more often hypertensive and less often smokers, were less physically active, had a lower HDL-C level, and a lower WH-ratio. Subjects in the category of ≥ 30 g alcohol per day were most

Table 1
Baseline characteristics by categories of alcohol consumption (g per day)

Alcohol category	0	<10	10–30	≥30
Alcohol intake (mean)	0	4.8	17.6	41.9
N	756	936	519	182
Age (years)	63.4 ± 7.2	61.2 ± 7.3[a]	60.3 ± 7.1a	59.7 ± 6.6a
Sex (% men)	25.0	45.5a	65.9a	74.2a
Prevalent diabetes (%)	13.4	7.5a	10.0	11.5
Fasting specific insulin (pmol/l)	78.6 (62.6–105.2)	77.3 (60.3–100.9)	74.5 (59.3–95.8)[a]	76.4 (59.0–96.4)
WH-ratio	0.88 ± 0.08	0.89 ± 0.09	0.91 ± 0.08	0.94 ± 0.09[a]
BMI (kg/m^2)	27.0 ± 4.0	26.3 ± 3.4[a]	26.2 ± 3.3	26.7 ± 3.0
Chol. (mmol/l)	6.74 ± 1.28	6.63 ± 1.13	6.58 ± 1.12	6.72 ± 1.07[a]
HDL-C (mmol/l)	1.29 ± 0.34	1.34 ± 0.37[a]	1.32 ± 0.37[a]	1.40 ± 0.41[a]
Triglycerides (mmol/l)	1.40 (1.00–2.00)	1.30 (1.00–1.80)[a]	1.40 (1.10–2.00)	1.50 (1.10–2.30)
Hypertension (%)	39.7	28.5[a]	26.6[a]	33.5
Prevalent CVD (%)	22.1	17.9[a]	13.9[a]	20.9
Smoking (%)	23.5	29.5	39.8[a]	49.5[a]
Sport (%)	19.7	30.7[a]	33.1[a]	29.1[a]

WH-ratio, waist to hip ratio; BMI, body mass index; Chol, cholesterol; HDL-C, high density lipoprotein cholesterol; CVD, cardiovascular disease; sport, active in sport activities; Data are presented as means ± SD, median (25–75th percentile), or proportion. Triglycerides and fasting specific insulin are tested with log-transformed data. All differences were tested adjusted for age and sex, and the level of significance was 0.05.

[a] Significantly different from non-drinkers, adjusted for age and sex.

often men (74.2%), had a higher WH-ratio (0.94), were more likely to smoke often (49.5%) and had a mean HDL-C level of 1.40 mmol/l (Table 1).

During the follow-up until January 1999 (mean 7.6, range 0.1–9.2 years), 268 subjects died (11.2%).

The association between alcohol consumption and mortality did not clearly differ between subjects with normal glucose levels and subjects with abnormal glucose levels. As shown in Fig. 1, subjects who consumed moderate amounts of alcohol (up to 10 g per day) had the lowest mortality rate. Due to the high absolute mortality risk of subjects with abnormal glucose levels, the risk difference between moderate alcohol consumption and non-drinking was higher (9.2 per 1000 person years) than in subjects with normal glucose levels (5.7 per 1000 person years).

In subjects with normal glucose levels the age- and sex-adjusted relative risk for all-cause mortality relative to the category of 10 g per day was 1.55 (1.04–2.32) for non-drinkers and 1.05 (0.64–1.72) and 2.10 (1.15–3.85) for those consuming 10–30 g per day, and ≥30 g per day, respectively. In subjects with abnormal glucose levels these RRs were 1.72 (1.05–2.82), 1.44 (0.84–2.47) and 2.08 (1.10–3.96), respectively. In these subjects, alcohol intakes higher than 10 g per day were thus associated with a steeper increase in mortality risk (Table 2). Additional adjustment for cardiovascular risk factors and other lifestyle variables slightly reduced the estimates (Table 2).

Of the 1322 subjects who did not have diabetes at baseline and who participated in the follow-up measurements, 131 (9.9%) had diabetes at the follow-up measurements. Fig. 2 shows the cumulative incidence of diabetes in categories of alcohol consumption. Subjects who consumed up to

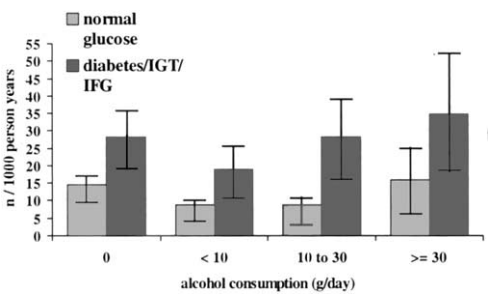

Fig. 1. All-cause mortality for categories of alcohol consumption stratified for subjects with normal and abnormal glucose levels.

Table 2
RR of all-cause mortality for categories of alcohol consumption, in subjects with normal and abnormal glucose levels

Alcohol (g per day)	0	<10	10–30	≥30
N	756	936	519	182
Normal glucose levels				
N	512	730	372	120
Model 1	1.55 (1.04–2.32)	1	1.05 (0.64–1.72)	2.10 (1.15–3.85)
Model 2	1.35 (0.90–2.03)	1	1.02 (0.62–1.67)	1.80 (0.98–3.31)
Model 3	1.38 (0.91–2.08)	1	1.02 (0.62–1.67)	1.63 (0.87–3.07)
Abnormal glucose levels (diabetes, IFG or IGT)				
N	244	206	147	62
Model 1	1.72 (1.05–2.82)	1	1.44 (0.84–2.47)	2.08 (1.10–3.96)
Model 2	1.62 (0.98–2.66)	1	1.52 (0.88–2.61)	1.87 (0.98–3.58)
Model 3	1.61 (0.98–2.65)	1	1.56 (0.90–2.69)	1.69 (0.86–3.32)

Model 1, adjusted for age and sex; Model 2, additionally adjusted for smoking, sport, prevalent CVD and hypertension; Model 3, additionally (with respect to model 2) adjusted for HDL-C, fasting specific insulin, triglycerides and WH-ratio.

10 g of alcohol a day had the lowest cumulative incidence: 8.0 versus 12.9% for non-drinkers ($P < 0.05$) and 9.8% for subjects who had a higher alcohol intake.

Subjects who consumed no alcohol at all had the highest risk for progression to diabetes. Relative to the category who consumed up to 10 g per day, the age- and sex-adjusted risk was 1.56 (0.99–2.48). The risk for subjects who consumed larger amounts of alcohol was 1.29 (0.80–2.06). Adjustment for possible confounders did not changed the estimates (data not shown).

4. Discussion

In the population of the Hoorn Study, moderate alcohol consumption (up to 10 g per day) was associated with the lowest risk for mortality and diabetes compared to non-drinking or a higher alcohol consumption. The absolute risk reduction for mortality was greater for subjects with abnormal glucose levels, but the increase in risks was steeper with increasing amounts of alcohol intake.

Information about alcohol consumption was obtained by a semi-quantitative food frequency questionnaire [23]. This method is liable to underreporting and inaccuracy [28,29]. However, the questionnaire we used was validated by comparison with a modified dietary history, and the Pearson correlation coefficient for alcohol consumption was 0.77 [23]. As the food frequency questionnaire contained many questions about nutrition habits with only a few of them about alcoholic drinks, it is less likely that selection bias occurred due to heavy drinkers not returning their questionnaires. In a large study in Germany, biological markers of alcohol consumption showed no evidence for underreporting of self-reported alcohol consumption [30]. As we divided alcohol consumption into four categories, minor inaccuracies in alcohol intake are not likely to have a large impact on our results. Some studies have argued that the reference category of non-drinkers has an increased risk for mortality, because this category is a mixture of lifetime abstainers and former-drinkers who because of illness ceased alcohol drinking [17,18]. We did not have information on

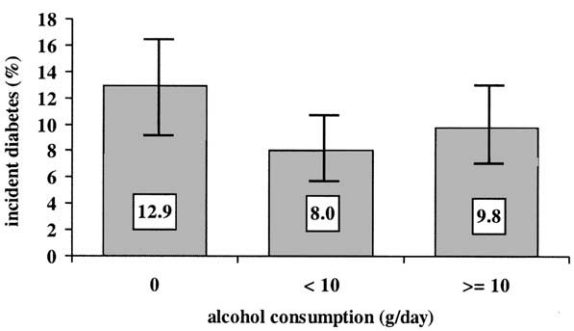

Fig. 2. Cumulative incidence of diabetes in categories of alcohol consumption.

ex-drinkers. However, in studies in which ex-drinkers were excluded from the category of non-drinkers, the lifetime abstainers still had higher mortality risk compared with moderate drinkers [3,11,31]. Furthermore, in the multivariate analyses we adjusted for prevalent cardiovascular diseases.

Previous studies that showed that moderate alcohol consumption was associated with a lower mortality risk have been performed mainly in the general population or in healthy subjects [1–4,31]. Three studies were performed among diabetic subjects [11–13]. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, the risk relative to lifetime abstainers was lowest for subjects drinking ≥ 14 g of alcohol a day (RR 0.21) [11]. In the Physicians' Health Study diabetic men who consumed alcohol daily had a relative risk of 0.42 for CHD mortality [12] and in the Nurses' Health Study the relative risk was 0.48 for those reporting usual intake (≥ 5 g per day) [13]. In should be noted that all these studies were conducted in the United States and that only a limited number of subjects had higher intakes of alcohol. In the Netherlands the range of alcohol consumption is much broader. In the present study, both for subjects with normal and for those with abnormal glucose levels mortality risk increased with higher intakes. The present study clearly indicates that in the high-risk group of diabetes, IFG or IGT, the absolute risk reduction with moderate alcohol consumption was larger. However, with higher alcohol consumption the risk increased faster compared with subjects with normal glucose levels, although the formal test on interaction did not reach statistical significance.

At baseline, 71.5% of the subjects invited from the general population participated in the Hoorn Study. Of the 2086 subjects who were invited for the follow-up examination, 1513 subjects participated (72.5%). As is frequently observed in population studies, the participants were younger (60.6 vs. 63.2 years), had a lower waist-to-hip ratio (0.89 vs. 0.90) and a more favourable lipid profile at baseline. Their alcohol consumption was 9.2 compared with 7.5 g per day of the non-participants. The baseline glucose levels of the participants were lower, which might have underestimated the cumulative incidence of diabetes.

The incidence of diabetes was lowest in the category of < 10 g alcohol a day. In a study among middle aged British men, the lowest risk for diabetes was seen in subjects who consumed 16–42 alcoholic drinks per week, corresponding to about 23–60 g per day [16]. Wei et al. observed the lowest risk with an alcohol intake between of 9–18 g per day, while higher intakes were associated with a twofold increase in risk [17]. However, in the latter study the definition of diabetes was based on fasting plasma glucose levels only.

As moderate alcohol consumption might be associated with a healthy lifestyle, we adjusted for the lifestyle variables smoking and physical activity. Nevertheless, this did not explain the observed association. Biological mechanisms that might explain the associations between moderate alcohol consumption, diabetes and mortality, might be the increase in HDL-C and in fibrinolytic activity, a decreased platelet aggregation and increased insulin sensitivity [5–7,14,15]. The adverse effect of high alcohol intake may be attributed to elevated triglycerides level [5,14], hypertension, a decreased insulin-mediated glucose uptake, liver cirrhosis and a decreased glucose tolerance [14]. In the present study, the adverse cardiovascular risk profile of subjects with abnormal glucose levels might explain the fast increase in mortality risk with higher alcohol consumption in these subjects. Future research on this topic is needed to further elucidate the mechanisms.

In conclusion, as moderate alcohol consumption might lower mortality and diabetes risk, moderate alcohol consumption should not be discouraged. However, subjects should also clearly be warned for the risks associated with over-consumption.

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